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Clinical findings in 25 patients with sinonasal or nasopharyngeal extramedullary plasmacytoma in a four-decade single-centre series

Seija I. Vento, MD, PhD[1], Pauli Vähämurto, MD[1,3], Kaija Silventoinen MD[1]; Marja-Liisa Karjalainen-Lindsberg, MD, PhD[2]; Susanna Mannisto, MD, PhD[3]; Sirpa Leppä, MD, PhD[3]; Antti A. Mäkitie, MD, PhD[1,4]

[1] Department of Otorhinolaryngology - Head and Neck Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[2] Department of Pathology, University of Helsinki and Helsinki University Hospital, Haartman Institute, Helsinki, Finland

[3] Department of Oncology and Research Program Unit, Medical Faculty, University of Helsinki and Helsinki University Hospital Cancer Center, Helsinki, Finland

[4] Division of Ear, Nose and Throat Diseases, Department of Clinical Sciences, Intervention and Technology, Karolinska Institutet, Karolinska University Hospital, SE-171 76 Stockholm, Sweden

Correspondence:

Seija Vento, MD, PhD

Dept. of Otorhinolaryngology - Head and Neck Surgery

Helsinki University Hospital

P.O. Box 263, FI-00029 HUH, Helsinki, Finland

E-mail: seija.vento@hus. fi

Tel: +358-50-42769618

INTRODUCTION

Plasmacytomas are malignant neoplasms of plasma cells classified as mature B-cell neoplasms [1]. Plasma cell neoplasms include extramedullary plasmacytoma (EMP), solitary bone plasmacytoma (SBP), multiple myeloma (MM), and the syndromes defined by the consequence of tissue immunoglobin deposition i.e. amyloidosis and light and heavy chain deposition diseases. EMPs are localized plasma cell neoplasms that arise in tissues other than bone [1]. The lesion can be either a primary plasmacytoma of the mucosa, unifocal or multifocal, with or without affected lymph nodes or extramedullary manifestations of MM [2]. EMP accounts for only 3-5% of all plasma cell neoplasms and 1% of all head and neck tumours but 80% of them originate in the head and neck region. However, they comprise only 4% of all non-epithelial tumours of the sinonasal tract [1, 3, 4].

Two thirds of EMP patients are male, and their median age is 55 years [1]. The disease is typically localized, and the incidence of lymph node involvement is 10-20% [5]. Fifteen to 20% of the cases progress to MM or regional disease [4]. MM is more common in SBP where the conversion rates vary between 48% and 85% [3, 4]. Radiotherapy is the treatment of choice but there is no consensus on the optimal radiation dose. Doses of > 45 Gy are considered to be safe but 35 Gy is found to be sufficient for small tumours [6]. In that study which included 14 patients with EMP in different soft tissue area, patients were treated with 35 Gy, and the only failed case was in a patient with a large primary tumour > 5 cm. In the study by Tournier-Rangeard et al. local control and disease-free survivals seemed to be dose dependent. The 5-year local control rate was 100% for the patients who received $\geq$ 45 Gy and 50% for the patients who received < 45 Gy [7].

In their 2004 guidelines, the UK Myeloma Forum recommends doses of 40-50 Gy [8]. Surgery is used alone or with pre- or postoperative radiotherapy in small or localized cases. Chemotherapy has only been used only in some rare cases [9, 10]. According the U.K. Myeloma Forum, chemotherapy should be considered for EMP patients if the tumour is > 5 cm, for high-grade tumours, for refractory and or relapsed disease and in therapy for MM [8].

Larger EMP series have been reported but these typically include tumours from the oropharynx, larynx, parotid gland, orbit, and neck [5, 10-15]. Also, many studies include patients with EMP and SBP together [11, 16, 17]. To our knowledge the largest study so far includes 68 solitary

EMPs with 37 cases in the sinonasal tract or nasopharynx [10]. The rarity and the long clinical course of this disease entity lead to difficulties in determining prognostic factors and in determining the optimal management.

In the present study, we have retrospectively analysed an institutional series of patients with sinonasal tract or nasopharyngeal EMP in order to delineate their main clinical characteristics and optimal management. We also emphasize this entity as a rare differential diagnostic alternative when a sinonasal or nasopharyngeal mass is encountered in patients with persistent nasal complaints.

PATIENTS AND METHODS

A retrospective review was performed of all patients diagnosed and treated for an EMP of the sinonasal tract or nasopharynx at the Departments of Otorhinolaryngology - Head and Neck Surgery and Oncology, Helsinki University Hospital (HUH), Helsinki, Finland between 1975 and 2013. The patients with a verified disease in the nasopharynx, nasal cavity or paranasal sinuses were identified from the files of the Department of Pathology, University of Helsinki. In addition, data for the same geographical area during this time period were collected from the nationwide Finnish Cancer Registry to ensure that all the patients diagnosed in the corresponding hospital referral area were included in the study (Malila N, personal communication, 2015). All plasmacytoma diagnoses were reviewed and confirmed by an experienced hematopathologist (M.-L.K.-L.). The study group consisted of 25 patients with adequate clinical and histopathological data available. Data on patient characteristics, and clinical and histological details were recorded. All patients had a minimum follow-up time of 27 months or until death. SPSS Statistics (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.) was used for statistical analyses. Institutional research approval was granted for the study.

RESULTS

The median age at diagnosis was 66 years (range, 36-80) and eighteen patients (72%) were male. The duration of symptoms prior to diagnosis was available for 23 patients (median 5 months; range, 0-24). Nasal symptoms were the most common (n=17, 68%). Thirteen patients

(52%) had bloody discharge, and 11 (44%) had nasal blockage. Six patients (24%) had eye symptoms. Three of them had double images, and two had lost their vision. Many patients had several of these symptoms (Table 1).

In nine patients (36%), the disease occurred in the nasopharynx including eight cases (32%) with nasopharynx as the single location. The nasal cavity was affected in 14 patients (56%) and it was in a single sinonasal location in 9 patients (36%). Paranasal sinuses were involved in 8 cases (32%) with 3 cases (12%) with paranasal sinuses as the single site. Seven patients (28%) with paranasal involvement had bone erosion in their orbits or skull base.

In 22 cases (88%) EMP was the primary plasma cell neoplasm. In total, four patients with primary EMP experienced progression to MM during the follow up and they all died from their disease. In two patients, systemic disease had been diagnosed with MM one year earlier, and they both died one to two months after EMP management with radiotherapy. One patient had two years earlier been diagnosed with non-Hodgkin lymphoma, and was then diagnosed first with EMP in the neck, and three years later in the tongue and nasopharynx. He was treated with radiotherapy but died 29 months later due to T cell lymphoma.

Four patients (16%) were primarily treated only with surgery. Two of the operated patients (tumour in the nasopharynx or in the nasal concha) had a local recurrence after two to three years, and both were successfully treated with radiotherapy and they died from an unknown or other cause 111 and 195 months later, respectively. For one patient with a septal lesion, surgery and postoperative radiotherapy were recommended but the free margins in the surgical tumour specimen were considered sufficient and the radiotherapy was not done. The patient died of another cause 40 months later without a local relapse. The last patient with a septal tumour has been followed for 27 months with no evidence of the disease reoccurring.

Altogether four of the patients received a combination of surgery and (chemo)radiotherapy. In two of these patients the first histology was ambiguous and after a wider surgical resection the margins were still non-radical. Despite postoperative radiotherapy or chemotherapy they both died either of MM or treatment-related cause, respectively. One patient received postoperative radiotherapy because of he was relatively young (41years) and he had an uneventful follow up for 89 months. In one patient, the tumour residual after radiotherapy was surgically removed from the nasal cavity and he had an uneventful follow up for 50 years.

Seventeen patients (68%) were primarily treated with only radiotherapy or

(chemo)radiotherapy. The mean dose was 44.7 Gy (median 50 Gy; range, 30-50). Eight patients (47%) had a complete response to primary radiotherapy and have been without local relapse or progression to MM with a median follow-up time of 89 months (range, 40-245). One patient had a complete response after receiving additional brachytherapy and has been uneventfully followed for 190 months. Five patients perished due to MM of these two patients had MM before EMP diagnosis and one had local spreading before MM. One patient developed an EMP recurrence eight months after radiotherapy and additionally a diffuse large B-cell lymphoma 19 months after primary EMP and died from the lymphoma. The other patients died either of treatment-related sepsis (one patient) or T-cell lymphoma (one patient).

Treatment, outcome, and follow-up data are shown in Table 2a-b.

In the whole series, 11 patients (44%) were alive with no evidence of disease after a median follow-up time of 78 months (range, 27 - 245). Three of these 11 patients had bone erosion to the orbit and one also to the lamina cribriformis, but they were successfully treated with radiotherapy and followed for 77, 78, 245 months, respectively (Figure 1 and 2 for one patient). Ten patients (40%) died from MM or other lymphoid malignancy after a median follow-up time of 23 months (range, 1-56). Four patients had died from other diseases with a median follow-up time of 105 months (range, 40-195).

The median age at diagnosis was 65 years for the patients who were free of the disease or had died from other reasons during this follow up and 68.5 years for those patients who had died from EMP, MM or other lymphoid malignancy.

In the statistical analyses significant differences were not observed in the patient characteristics between the group that was treated with radiotherapy and the group that was not treated with radiotherapy. In multivariate analyses age at diagnosis, location, sex or treatment did not have an impact on overall survival (OS).

DISCUSSION

We present a single-institution review of 25 patients with sinonasal tract or nasopharyngeal EMPs over almost four decades. This is a large population-based analysis that includes

practically all the patients diagnosed with sinonasal or nasopharyngeal EMP in this referral area of 1.6 million inhabitants covering almost one third of the Finnish population. To ensure that all the patients were included, we also received data from the nationwide Finnish Cancer Registry, which has been functioning for over six decades and has complete coverage of the cancer cases in Finland.

The present study comprises one of the largest clinical series of patients with EMP only involving the sinonasal tract and nasopharynx. In a Canadian study of 68 solitary EMP cases in the head and neck area 37 EMP cases were diagnosed in the nasal cavity, paranasal sinuses or nasopharynx [10]. The sinonasal tract was the most common site. Fifty-seven percent were treated with radiotherapy, 12% with surgery, 21% with surgery and radiotherapy and four percent with chemoradiotherapy in their series. The 5-year local-recurrence-free survival was 81%. There was a trend towards improved local recurrence-free rate in patients with primary radiotherapy. The 5-year regional-recurrence-rate was five percent. MM developed in 23% and the 5-year survival was 76% [10]. In another study of 67 EMP cases of the head and neck at 23 Japanese institutions 43 EMP cases examined were in the sinonasal tract or pharynx. The overall 5- and 10-year survival rates were 73% and 56%, respectively and the cause-specific 5- and 10-year survival rates were 82% and 76%, respectively [15]. The disease progressed in 36% of patients and 12% developed MM. Every patient received radiotherapy and in 28% of them surgery preceded radiotherapy. In eight percent radiotherapy was combined with chemotherapy and in six percent radiotherapy was followed by surgery with or without chemotherapy. Radiotherapy was quite effective but radiotherapy combined with surgery produced better survival rates [15].

In a review of 67 studies including 175 EMP sinonasal patients, radiotherapy was the most common treatment modality. Radiotherapy alone was used in 89 cases (51%) followed by a combination of surgery and radiotherapy [18]. At the median follow-up of 39 months 72% of patients were alive, independent of treatment modality. Radiotherapy combined with chemotherapy was rarely used but had the best outcome with 89% (8/9) of the surviving patients [(18)]. In this review, of the three most common treatments (radiotherapy alone, surgery alone, combination surgery and radiotherapy), radiotherapy alone was the most common treatment, but a combination of surgery and radiotherapy had the best outcome [18]. The majority of patients who developed MM had received radiotherapy alone as their primary management. The authors concluded that surgery should be considered for small tumours [18].

The presenting symptoms in the present series started five months (median) prior to EMP diagnosis. Nasal blockage and bloody discharge were common symptoms but 24% had eye or neurological symptoms. Seven patients (28%) with paranasal involvement had bone erosion to their orbits or skull base. As the symptoms may be vague, they can be present for months or years prior to diagnosis [19].

Local recurrences as well as progression to MM in this cohort occurred within three years from the initial EMP diagnosis. In addition, one patient developed a diffuse large B-cell lymphoma within the same time period. Two years before the EMP, one patient had been diagnosed with Hodgkins lymphoma, and was then diagnosed first with EMP in the neck, and three years later in the tongue and nasopharynx and then further developed T-cell lymphoma. In our study, four primary EMP patients developed MM, three of which were primarily treated with radiotherapy and one with surgery followed by radiotherapy for local relapse.

It is difficult to determine the optimal therapy for EMP because of the small number of patients in most studies. Further, as in most retrospective study settings, there is a selection bias for small tumours being treated with surgery. However, radiotherapy doses over 45 Gy are considered safe and effective [6, 7]. The mean dose 44.7 Gy (median 50 Gy; range, 30-50) used in our cohort is in accordance with this. The role of systemic therapy is unclear except for the cases that progressed to MM. It has been suggested by the UK Myeloma Forum that chemotherapy should be considered in EMP treatments in cases with tumour diameters over 5 cm, high-grade tumours, as well as refractory and/or relapsed disease, and for patients with simultaneous systemic MM [8].

Our findings regarding male predominance (72%) and median age (66 years) are in accordance with the existing reports [10, 15, 18]. It has been previously reported that the overall survival is better for younger patients ($\leq$ 60 years) and for patients with tumour diameter less than 4 cm [(16)]. In our study the median age at diagnosis was 65 years for the patients who were free of the disease or had died of another cause during the follow up and 68.5 years for those patients who had died of EMP, MM or another lymphoid malignancy.

According to previous reports the rate of conversion of EMP to MM is 15% to 20% [(4)]. In a study of 17 EMP patients, 29% of them progressed to MM [(14)]. In our study the conversion rate was 17% (4/23). Additionally, two patients have been followed for 27 to 44 months with MGUS without progression to MM. Additionally eight percent (2/25) were diagnosed with MM

approximately one year prior to EMP. The conversion risk is at its highest during the first two years but it has been noted up to 15 years later [10]. When conversion to MM has occurred, less than 10% of patients will survive 10 years [2, 10]. There is some controversy whether EMP and MM are different phases of the same disease or two different clinical entities [10]. In our study, all six MM patients died of their disease.

Radiotherapy combined with surgery was the only significant prognostic factor in the study by Sasaki et al. [15]. Tumour size, age, sex, radiotherapy dose and chemotherapy did not influence the prognosis [15]. In another study radiotherapy and serum β2 microglobulin <3.5 mg/L were favourable prognostic factors for local control, MM-free survival, and progression-free survival in patients with EMP [17]. In the present study no prognostic clinical factors were found by Cox analyses. Plasmacytomas treated with surgery combined with radiotherapy were localized, whereas tumours treated with radiotherapy had typically spread to adjacent structures and consequently, surgery was not considered for the primary treatment or it could have resulted in positive resection margins. Nonetheless, one patient had plasmacytoma in all his right paranasal sinuses and there was also bone destruction to the orbit and lamina cribriformis. This patient was treated only with radiotherapy and he was still disease free after 20 years. Two other patients had tumours in their maxillary sinus with bone destruction also in their orbits and they were also disease free after six years. The remaining four with paranasal involvement with bone erosion to their orbits or skull bases died. Two of them died from MM, one had already earlier diagnosed MM and on died from sepsis. This proves that even large tumours can be highly radiosensitive, and the local spreading of the disease does not alone predict its prognosis.

Ghazizadeh et al. published a case report of a 24-year-old male with a large right maxillary tumour with bone destruction in the medial and lateral walls [20]. The tumour was radioresistant but responded to surgical treatment followed radiotherapy and was followed for one year without relapse [20]. One of our patients had surgical treatment for a remnant tumour after radiotherapy with complete response and has been followed for 50 months without local recurrence or developing MM.

The present work has the limitations associated with retrospective studies. Symptoms, laboratory findings, histopathology, treatment and survival data were recorded from patient files and some data on certain parameters were not available for all the patients. Imaging techniques have developed significantly during the past decades and have increased the information on the distribution of the disease but they were not available for the first cases in

this series.

CONCLUSIONS

EMP in the sinonasal tract and nasopharynx is a rare condition to be considered as a differential diagnosis for patients with a wide variety of continuous obstructive nasal symptoms. Radical treatment and long-term survival are achievable in this patient population. Our study supports radiotherapy as a treatment of choice, however for small tumours surgery alone or combined with radiotherapy may be considered. In this study, local recurrence as well as conversion to MM occurred within three years of primary EMP diagnosis. Local relapses were successfully salvaged, but all patients whose disease developed to MM or subsequent other lymphoid malignancy died from their disease. No prognostic factors were discovered. .

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DISCLOSURE STATEMENT

No conflict of interest to declare.

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